

REMARKS

Initially, applicants request that a personal Interview be granted to applicants' representative to discuss the situation set forth below and discuss the scope of claims which would be maintained for allowability in view of the clarified showing. Applicants urge the Examiner to contact the undersigned to arrange the Interview when the case is first taken up for substantive review before issuing an action. Applicants will also monitor the status of the application and attempt to contact the Examiner at that time. Of course, if the Examiner is in full understanding of the situation and finds the above claims allowable, then applicants are willing to forego the Interview.

Applicants are filing this Reply with an RCE after the Notice of Allowance in order to point out an erroneous assumption made in the prior prosecution, which is now sought to be corrected.

In the Declaration under 37 C.F.R. §1.132 of Dr. Fricke filed with the Reply of February 15, 2008, data was presented comparing compositions wherein the vehicle was recited in terms of the % of castor oil (CO) and benzyl benzoate (BB). The data showed the advantage of the 37%CO/63%BB vehicle over 50%CO/50%BB and 60%CO/40%BB vehicles when formulated in accordance with the claimed invention. The declaration did not state whether the percentages given were by weight or by volume. Applicants' representatives assumed that the percentages were by volume and argued based on this assumption in the reply submitted with the declaration and in subsequent replies. Ultimately, based on this assumption, applicants narrowed the claims to recite that the vehicle contained a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume. If the assumption had been correct, then the ratio of 1:1.7 by volume would have

exactly matched the 37%CO/63%BB showing. However, it was just recently discovered that the percentages in the declaration were percentages by weight, not volume. The declaration is not incorrect but, rather, ambiguous, and the ambiguity led to the incorrect assumption.

Applicants' arguments in the Replies filed February 15, 2008, November 3, 2008, and February 10, 2009, are based on the incorrect assumption. Specifically, applicants argued that the declaration showed the advantages for a vehicle having 37% by volume of CO and 63% by volume of BB compared to vehicles having 50 vol% CO/50 vol% BB and 60 vol% CO/40 vol% BB. But the data was actually in terms of weight%. When the weight% is converted into vol% the numbers change. A new 37 C.F.R. §1.132 Declaration of Dr. Fricke is provided herewith to replace the previous one. It explicitly sets forth that the percentages are by weight and provides a conversion from weight% to vol%. The embodiment which shows the unexpected advantages is of a vehicle having 37 weight% CO and 63 weight% BB, which converts to 40.7 vol% CO and 59.3 vol% BB.

As a result of the above, it is necessary to amend the claims to recite the nature of the castor oil/benzyl benzoate vehicle in terms of vol% of the castor oil rather than in terms of the ratio of the vehicle components. It should be clear that the 1:1.7 by volume ratio does not reflect the embodiment for which the advantages are shown by the declaration. Applicants obviously want the claims to cover the advantageous embodiment and obviously the claims must be commensurate in scope with the actual showing of unexpected advantages for the showing to support patentability of the claims. Therefore, the claims are amended to recite that the "vehicle contains castor oil in a concentration of 40 to 45 vol%." This range reflects the support provided by the disclosure (as pointed out below). Applicants believe the showing of unexpected

advantages for the 40.7 vol% CO provides a reasonably representative basis for patentability of the amended claims. A dependent claim reciting that the vehicle contains castor oil in a concentration of about 40 vol% is also provided and intended to encompass the 40.7 vol% value.

Support for the claim amendments is found in the specification at page 8, lines 30-34, which recites ranges where endpoints at 40 and 45 vol% are explicitly recited; see also In re Wertheim, 191 USPQ 90, at 96 (CCPA 1976); and In re Voss, 194 USPQ 267, 271 (CCPA 1977), supporting that narrower ranges are necessarily implicitly described within an explicit broader range recitation. Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

Applicants urge that the 37 C.F.R. §1.132 Declaration of Dr. Fricke supports the nonobviousness of the instant claims and that the claims should not be subject to the previous grounds of rejection under 35 U.S.C. §103, as being obvious over WO 95/12383 in view of Riffkin (J.Pharm.Sc.).

As for the comparative showing in the new declaration, the previous finding of allowability was based on applicants' showing of the unexpected advantages of the claimed invention as proof of nonobviousness. It is urged that, with the clarification made by the new declaration, the showing of nonobviousness is representative of the unexpected advantages of the current claims and commensurate in scope with the claims. The declaration provides a side-by-side comparison of the stability of compositions according to the claimed invention with compositions otherwise the same but having higher amounts of castor oil, such as taught by Riffkin. Multiple ampoules of compositions containing testosterone undecanoate, benzyl

benzoate and castor oil were tested side-by-side for stability (lack of precipitate crystals) over 34 days. One set of ampoules contained 60 weight% castor oil (i.e., 63.7 vol%), one set 50 weight% (i.e., 53.9 vol%) and one set 37 weight% (i.e., 40.7 vol%). All of the ampoules which contained 37 weight% castor oil (i.e., 40.7 vol%) – and thus are representative of the claimed invention – maintained stability with no precipitate for the full 34 days. For the compositions which contained 50 weight% (i.e., 53.9 vol%) and 60% weight% (i.e., 63.7 vol%) castor oil, most of the ampoules lost stability before 34 days.

The advantage in stability of the compositions, when using a lower amount of castor oil as recited in the instant claims, could not have been expected from the prior art. Neither reference teaches any advantage in stability for its compositions based on the proportions of the vehicle components, or otherwise. Further, to the extent Riffkin suggests to use castor oil in the WO '383 compositions, it fails to teach or suggest amounts as low as in the recited claims. It should be pointed out here that Riffkin also does not indicate whether the % numbers in its data are by vol% or weight% so its teachings are ambiguous and sheds some doubt on its applicability. Even if it assumed that the % numbers recited by Riffkin are vol%, the lowest amount of CO in a vehicle used together with a steroid taught by Riffkin is 52% (see Tables V and VI) and the CO amounts range up to 80%. (Riffkin also presents a 50/50% mixture of CO and BB in Table IV but not mixed with a steroid.) Thus, if Riffkin is in vol%, applicants' comparison in the declaration of an embodiment of the claimed invention at 40.7 vol% CO to the embodiment of 53.9 vol% CO is reasonably representative of the Riffkin prior art at 52 vol% and even the non-steroid embodiment at 50 vol%. If the Riffkin % numbers are by weight, the Riffkin embodiment with the steroid converts to 56.0 vol% CO and the embodiment of Riffkin

without the steroid and converts to 53.9 vol% CO (i.e., exactly what the declaration compares). Thus, regardless of how Riffkin is interpreted, the advantage in stability of the solutions according to applicants' invention using a lower amount of castor oil was clearly unexpected over the prior art teachings.

Further, the showing is commensurate in scope with the claims. The law and PTO guidelines only require that the showing be reasonably representative of the advantage(s) of the claimed invention over the cited prior art; see, e.g., In re Kollman, 201 USPQ 193 (CCPA 1979); In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980); and MPEP §2145. The closest actual prior art embodiment in Riffkin which provides the basis for comparison would be the compositions which contain a steroid and the lowest vol% of CO in such embodiment is either 52 vol% or 56 vol% and the embodiment applicants' compared of 53.9 vol% is reasonably representative of both. The embodiment within the claimed invention which was compared to this is of 40.7 vol% CO, which is reasonably representative of the claimed range of 40-45 vol%. The 40.7 vol% value is much closer to the 45 vol% maximum than the lowest CO vol% embodiment with steroid of Riffkin. As noted above, the standard at issue is a "reasonable" one, not a strict one and the showing related to a single embodiment is reasonably representative of the still narrow 5 vol% scope of the claimed range. The commensurate nature of the showing is further bolstered by the fact that Riffkin's other embodiments use a much higher vol% of CO, thus, the overall teachings of Riffkin points to amount much above its minimum rather than below it.

The declaration provides additional data comparing the stability of solutions containing castor oil compared to peanut oil and miglyol solutions further bolstering the case for

nonobviousness. These comparisons clearly show that castor oil is advantageous over these other oils. Thus, the comparison also shows the advantage in stability of the solutions of the claimed invention using castor oil over those having the first-listed preferred oil of WO '383, i.e., peanut oil.

The above-discussed advantages discovered by applicants were discussed in applicants' specification (page 10, lines 24-33):

The compositions of the invention are chemically stable with respect to the testosterone esters. That is to say that degradation products could not be detected after long term storage (such as after 7 weeks or 17 weeks or even longer) at conditions normally known to accelerate degradation processes, such as variations in temperatures, high and low temperatures and various relative humidity. For example, less than 1% by weight of degradation products of testosterone esters is present after storage of the composition for at least 7 weeks, such as for 16 or 17 weeks, for 6 months, or for 9 or 12 months at 40 °C and 25 % RH in darkness. Preferably, less than 0.5 % w/w, such as less than 0.2 % w/w of degradation products of testosterone esters is present after storage at the above-mentioned conditions.

The references do not teach or suggest anything regarding such the advantageous stability properties. Thus, the advantages are clearly unexpected from the prior art and provide a clear and convincing case for nonobviousness. For all of the above reasons, it is urged that this data in the declaration provide clear and convincing proof of the unexpected advantages of the claimed invention and thus the nonobviousness of the claimed invention.

Applicants further submit that the references fail to support a prima facie case of obviousness in the first instance or, alternatively, that any such case is a weak one which makes the showing of nonobviousness even more convincing.

WO '383 discloses an injectable solution of testosterone undecanoate with an injectable

plant oil and/or benzyl benzoate. WO '383 provides no suggestion to use castor oil as the plant oil in its compositions. To the contrary, at page 4 of the publication, WO '383 recites the possible use of peanut, soy, sesame, tea or olive oils. WO '383 also provides no suggestion as to the relative amounts of the plant oil and benzyl benzoate. Particularly, there is no suggestion of a composition of testosterone undecanoate contained in a vehicle comprising castor oil and benzyl benzoate where the castor oil is in a concentration of 40 to 45% by volume in the vehicle, as recited in the current claims.

The Office action alleges that it would have been obvious to one of ordinary skill in the art to modify the teachings of WO '383 in view of Riffkin since Riffkin teaches the use of a vehicle having castor oil and benzyl benzoate in defined relative amounts (see the above discussion of the ambiguity of whether the amounts are in vol% or weight%) for delivering steroidal compositions parenterally. Riffkin discusses the use a combination of castor oil and benzyl benzoate as a vehicle for steroid hormones generally. However, Riffkin discloses no such combination of a vehicle with a testosterone ester. Riffkin discloses 5 examples of vehicles with castor oil and benzyl benzoate without a steroid in Table IV, page 893, and 6 examples of vehicles with castor oil and benzyl benzoate containing a steroid in Tables V and VI, page 894. In the vehicles where a steroid is contained, the amount of castor oil ranges from 52 to 80%, i.e., well above the 45 vol% maximum recited in the instant claims (and even higher if the % are by weight).

Applicants respectfully submit that one of ordinary skill in the art would not have been motivated or otherwise had a reason to modify the compositions of WO '383 in view of Riffkin to provide a composition meeting the requirements of the instant claims. If one of ordinary skill

in the art were to modify the WO '383 compositions in view of Riffkin, they would use castor oil as the plant oil in an amount of 52-80% in the composition according to Riffkin's teachings. Such a composition would not meet the recitations of the instant claims, i.e., a vehicle comprising castor oil in a concentration of 40 to 45% by volume. There are no other suggestions from the cited references to provide a composition, as claimed, having this amount of castor oil.

It was alleged in the previous Final office action that "optimization of the amount of excipients is considered obvious as being within the purview of the skilled artisan." However, there is no factual basis on the record to support that lowering the amount of castor oil would result in some optimization. In order to support obviousness to modify an amount of a component in a composition for purposes of optimization, there must be some basis provided on the record that the modification of the amount would optimize some aspect of the composition. There is no basis to assert such here. The Office action merely alleges optimization but indicates no objective – based on the references' teachings – for such optimization or what aspect is intended to be optimized. Further, no reference of record provides any support that lowering the castor oil amount would optimize the composition in any way. To the contrary, the only teachings of record regarding an amount of castor oil come from Riffkin which teaches a range of 50 or 52% as a minimum and up to 80%. Since Riffkin clearly pointed one of ordinary skilled in the art to this amount range, the only reasonable conclusion such skilled artisan could draw from the record here is that 50 or 52% as a minimum up to 80% is the optimal range and other amounts would, therefore, be less than optimal. There is certainly no direction from the cited prior art that lowering the amount of castor oil would lead to optimization or what property would be optimized. The only suggestion of this comes from applicants' own teachings and data.

Additionally, no basis in the law is cited for the proposition that “optimization of the amount of excipients is considered obvious as being within the purview of the skilled artisan.” The context of the statement in the Office action and the failure of any factual support for it, leaves the impression that it is allegedly per se obvious to modify the amounts of a reference composition to achieve some undefined “optimization.” If this is what is being alleged, it is clearly contrary to the law. Lacking any evidentiary support, the alleged general optimization argument is merely a conclusory statement of the type the Supreme Court recently cautioned against use to support an obviousness rejection; see, KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, at 1396 (2007), stating: “rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” A general statement that some undefined optimization would be obvious is not a sufficient rational underpinning to support the rejection.

For all of the above reasons, it is urged as a separate basis for patentability that the cited references fail to establish a prima facie case for obviousness. Thus, the rejection under 35 U.S.C. §103 should be withdrawn for this additional reason.

For all of the above reasons, it is urged that the combined teachings of WO ‘383 in view of Riffkin, particularly when considered in light of the declaration evidence of nonobviousness, fail to render the claimed invention obvious to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 should be withdrawn.

It is believed that the claims are in condition for allowance. However, the examiner is

kindly invited to contact the undersigned by telephone to discuss matters which may further the prosecution of this application or facilitate the allowability of some or all of the claims herein.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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